Current Practice

Malabsorption

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(Last week the examination and investigation of patients with malabsorption were discussed. This week the clinical syndromes are described and their treatment outlined.)

Clinical Syndromes

Pancreatic Insufficiency

Steatorrhoea is often gross and the diagnosis may be suggested by the presence of abdominal pain and diabetes. Provided that the underlying cause is not debilitating patients retain their appetite, so that weight loss may not occur. Anaemia, osteomalacia, and a bleeding tendency are relatively uncommon. Xylose absorption and jejunal biopsy are usually normal. Glucose tolerance may show a diabetic curve. Calcification may be seen on an abdominal radiograph. The diagnosis may be proved by a Lundh test, which involves the measurement of trypsin in the duodenum after feeding a test meal, and clearly separates steatorrhoea of pancreatic origin from that due to other causes. Estimation of faecal enzymes is again coming into favour, and estimations of chymotrypsin concentrations may act as a reliable screening test in adults as well as children.

Treatment is by a low fat, high protein diet. Pancreatic extracts may be unpleasant to take and large quantities are required to fully replace normal pancreatic secretion. At the moment there is little information on the intraluminal concentrations attained after oral therapy, and the small doses often prescribed may be without effect.

Liver Disease

Obstructive jaundice causes malabsorption in which the fat-soluble vitamins and cholesterol are affected more than triglyceride. Anicteric liver disease may present as diarrhoea and steatorrhoea with minor changes in jejunal histology and otherwise normal small bowel function. Infectious hepatitis is associated with an inflammatory lesion of the jejunal mucosa which may play a part in the production of steatorrhoea and diarrhoea.

Coeliac Disease

This is the commonest form of generalized malabsorption in temperate climates. It occurs in children and adults and may even present for the first time in the elderly. The condition is caused by a toxic peptide present in the gliadin fraction of the wheat protein, gluten, but the mechanism of its action is unknown. It is diagnosed by the appearances of the jejunal biopsy together with a favourable response to a gluten-free diet.

The clinical manifestations of coeliac disease are legion and can include all the gastrointestinal and nutritional features mentioned before (Table II); symptoms are often not florid and may be absent. It is not known why patients whose dietary intake and biopsy appearances are identical should vary so much in their clinical picture. Most patients present with only a few of the listed features, of which anaemia is the commonest. It is usually due to a mixture of iron and folate deficiency, but some degree of vitamin-B_{12} deficiency is present in 30% of cases. Iron deficiency is usually refractory to treatment and may occur in the absence of steatorrhoea. Sideroblastic anaemia has been described. Disturbances of calcium and bone metabolism are common and osteomalacia can occur in the absence of steatorrhoea; it may be refractory to therapy with vitamin D until gluten has been withdrawn. A variety of skin changes are common and may respond to a gluten-free diet. Rare complications include the development of alimentary carcinomata and lymphomata, various neurological syndromes, and intestinal ulceration leading to perforation, stricture, or haemorrhage.

Jejunal biopsy is essential for diagnosis. Macroscopically the villi may show varying degrees of damage in which stunting, broadening, and fusion proceed to formation of ridges and convolutions, which finally disappear altogether to leave a flat mucosa. Histological examination shows abnormal villous architecture, damage to epithelial cells and their microvilli, and varying degrees of inflammatory cell infiltration of the lamina propria. These changes are not specific to coeliac disease and occur in tropical sprue and in some cases of ulcerative colitis, skin disease, and carcinoma. The mucosal damage is always greatest in the upper small bowel and decreases towards the ileum. Extensive lesions always result in gross forms of malabsorption owing to loss of ileal reserve. Until recently it has been assumed that the damage is uniformly severe at each level of the intestine, but multiple biopsies have now shown that variations may occur and single biopsies may not be sufficient for diagnosis.

Treatment is by withdrawal of gluten or administration of nutritional supplements. The former is preferable, since it should improve the absorptive function of the bowel so that deficiencies can be corrected from the diet without supplementation. There is also suggestive evidence that malignancy is less likely to supervene on a gluten-free diet, but other complications have not been shown to be lessened. Remission often starts within a few days, though it may take up to one year for full benefit to be obtained. Improvement occurs in appetite, weight, mental state and gastrointestinal symptoms; the histological response is much slower.

Between 70% and 80% of patients respond to the diet. Failure may occur for several reasons. The patient may not stick to the diet; a second disease—for example, pancreatic insufficiency—may be present; there may be complications such as malignancy and ulceration; or the jejunal atrophy may be secondary to another lesion and not due to coeliac disease.

Exclusion of milk from the diet and treatment with broad-spectrum antibiotics or steroids may help in certain refractory cases, although steroid therapy has a high rate of complications.

The alternative method of treatment is by the administration of nutritional supplements, which are usually combined with

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a low fat diet. Iron and folic acid are needed most frequently. If this form of therapy is employed the patient should be regularly reassessed, since absorption remains impaired. The deficiencies may be refractory to treatment ; or other nutritional deficits may appear.

Tropical Sprue

The aetiology of this condition is unknown. It is now being seen more frequently in temperate climates in patients who have come from endemic areas. Some will complain of residual symptoms following a more acute attack in the tropics, whereas others will have developed symptoms for the first time after leaving the area. The latent period before development of symptoms after moving to a temperate climate may be very long, and intervals of up to 15 years have been recorded.

Acute sprue in the tropics presents with gastrointestinal symptoms made worse by food. Diarrhoea is common, but in only a third of cases are the stools frothy or fatty. Other features of the acute stage are anorexia, weight loss, glossitis, epigastric discomfort, distension, flatulence, and heartburn. Nausea, vomiting, oedema, and mental disturbances occur less frequently. Anaemia is present early. This stage progresses to a subacute one in which nutritional deficiencies become more prominent.

Chronic sprue is the final stage of the process of the disease and is the form seen in temperate regions. It presents as a megaloblastic anaemia, which is often due to vitamin-B_{12} deficiency. Abdominal symptoms are variable and need not dominate the picture. Thus a subject may complain only of slight diarrhoea and abdominal distension.

The main problem is to separate the condition from coeliac disease. The duration of symptoms is shorter ; they have often been present for less than six months when the patient first seeks medical advice. The abnormalities found on radiography and jejunal biopsy are similar in both diseases but less severe in sprue ; for instance, a convoluted mucosa is common whereas a flat mucosa is rare. Sprue affects the entire length of the small intestine, and this is reflected by vitamin B_{12} malabsorption in all cases—serum B_{12} levels are subnormal. Anaemia is therefore due to both vitamin B_{12} and folate deficiency. Subnormal values of serum iron, calcium, and albumin are less common than in coeliac disease.

In acute sprue there is no response to a gluten-free diet, but treatment with antibiotics, folic acid, and vitamin B_{12} produces great initial improvement. The long term prognosis is less good, and many patients have to be managed on a low-fat, high-protein diet with vitamin supplements, especially folic acid and vitamin B_{12}. However, antibiotic therapy may produce gratifying results even in chronic sprue.

Whipple's Disease

This is a rare disorder predominantly affecting middle-aged men. The condition should be suspected if malabsorption is associated with arthralgia ; other features include fever, pigmentation, abdominal pain, polyserositis, and peripheral lymphadenopathy. Diagnosis is by jejunal biopsy. The disease appears to be due to a low-grade bacterial infection, and malabsorption is due to infiltration of the lamina propria with macrophages and more distant lymphatic obstruction. Treatment is by a prolonged course of broad-spectrum antibiotics and is curative.

Systemic Sclerosis

Fibrosis in the wall of the bowel gives rise to adynamic areas and stasis. Malabsorption may occur and appears to be due to an abnormal bacterial flora. Gross abdominal distension and bouts of apparent intestinal obstruction with visible peristalsis may be present in the absence of skin changes. However, Raynaud's phenomenon is nearly always present. Minor small bowel changes occur very frequently but are asymptomatic. Diagnosis is by radiology, but duodenal biopsy may show fibrosis around Brunner's glands. Jejunal biopsy is normal. The malabsorption will respond to antibiotics. Steroid therapy is valueless.

Disaccharidase Deficiency

The main sources of dietary carbohydrate are the complex sugars starch and glycogen, and the disaccharides sucrose and lactose. Initial digestion of the two polysaccharides occurs in the lumen of the gastrointestinal tract, and the products are mainly the disaccharides maltose and isomaltose. The final step in digestion of disaccharides takes place on the brush border of the intestinal mucosal cell. The main enzymes concerned are maltase, isomaltase, sucrase, and lactase, which split the appropriate disaccharides into monosaccharides, which are then pumped into the mucosal cell by a specialized mechanism.

Congenital Deficiency.—It is not surprising that children have been discovered who are lacking in one or other of the enzymes. The main clinical conditions result from absence of lactase or a combined sucrase-isomaltase deficiency. These children present in the neonatal period with acid diarrhoea, failure to thrive, dehydration, and malnutrition. Treatment with a diet which excludes the offending disaccharide or its precursor improves growth and diminishes symptoms. In adult life such subjects can partly outgrow their symptoms, though they are still unable to absorb the disaccharide. Occasionally sucrase-isomaltase deficiency is a cause of diarrhoea in adults.

Constitutional Hypolactasia (Acquired Deficiency).—Lactase deficiency in older children and adults is quite a different problem The symptoms are variable and less severe. Diarrhoea, abdominal colic, borborygmi, and distension may follow ingestion of milk. Similar symptoms may be present in other subjects who are unable to relate them to milk. A further group may be asymptomatic and some may even be able to tolerate large amounts of milk. The severity of the symptoms depends on the amount of lactose in the diet and the variable response of the colon to the stimulus of the unabsorbed free sugar and its fermentation products. When a large lactose load is ingested there is a high concentration of unabsorbed sugar in the small intestinal lumen, which attracts fluid by osmosis and so behaves like a bulk purgative, sweeping water, electrolytes, and occasionally fat and protein down the intestine. Such an episode is uncommon on a normal diet, since the concentration of lactose in milk is not high (40 g./litre). In most subjects lactose forms only a small proportion of the dietary carbohydrate and produces only recurrent minor symptoms throughout the day, which are probably the result of bacterial fermentation of lactose in the colon to produce short chain organic acids which irritate the large bowel.

Diagnosis is suggested by a flat lactose tolerance test (see above), which produces diarrhoea, borborygmi, and abdominal pain in 70% of patients. Absorption of glucose and galactose is normal. Other screening tests of absorption and nutrition are normal. Jejunal biopsy shows no anatomical abnormality, and assay of the disaccharidase content of the specimen confirms the diagnosis.

Constitutional hypolactasia has now been found in many different parts of the world. There is a very high incidence (up to 90%) in certain racial groups such as Negroes and Greek Cypriots, although in Northern Europeans the incidence is probably about 10%. In affected populations it seems that there is a gradual regression of lactase activity as maturation proceeds, since there is a normal lactase concentration in the neonatal period. This is comparable with most animal species,

and it can be argued that it is those who retain lactase activity who are abnormal.

The clinical significance of lactase deficiency has probably been overstressed in the past few years. It must be very rare for lactase deficiency to be the sole cause of severe diarrhoea as a presenting symptom. Moreover, since hypolactasia is a common finding, it should not be used as an explanation for other major symptoms such as marked weight loss or nutritional disturbance, when another cause should be sought. Lactase deficiency has been described in association with a number of other diseases, including ulcerative colitis, Crohn's disease, infectious hepatitis, and febrile illnesses. This association probably reflects the high incidence of the defect in any population. However, the symptoms of these diseases may be made worse by dietary lactose, or the development of the disease may render a previously compensated subject intolerant of milk.

Secondary deficiency occurs when the intestinal mucosa is damaged by such conditions as coeliac disease, tropical sprue, and infections. Depression of the activity of all enzymes of the mucosal cell occurs in proportion to the severity of the damage. The condition is reversible when the underlying disease heals. It is not usually functionally significant in adults, but in neonates and young children selective restriction of dietary sugars is often beneficial.

Protein-losing Enteropathy

The hypoalbuminaemia in most malabsorption states is not only due to malabsorption of protein or deficient intake. Studies with radioactive labels on albumin and other molecules of similar size have shown that there is often a concomitant increased rate of destruction due to leakage of albumin into the bowel lumen, where it is degraded. This is an exaggeration of the normal mechanism for albumin breakdown, and under these circumstances the liver is unable to compensate by increasing albumin synthesis.

This phenomenon of protein loss can occur in a pure form, when it is analogous with the nephrotic syndrome, or can be complicated by various forms of protein deficiency due to associated anorexia and malabsorption, so that wasting and skin changes may be more obvious as well as other signs of malnutrition. For example, in coeliac disease a degree of protein loss accompanies a generalized malabsorption defect, but peripheral oedema is not common, though it may occur transiently during therapy. In contrast, in disturbances of the lymphatic circulation, such as intestinal lymphangiectasia, oedema predominates; massive enteric protein loss results in hypoalbuminaemia upon which steatorrhoea and calcium malabsorption may be superimposed owing to obstruction to fat transport in the intestinal lymphatics. Thus in many patients the hypoalbuminaemia cannot be overcome by increased dietary protein.

Treatment

Complete diagnosis of the cause of malabsorption should always be attempted in case specific therapy is available. Careful screening for all possible nutritional defects is important so that precise replacement therapy may be given. Blunderbluss therapy with vitamins is to be deplored. General principles of treatment are laid out in Table III.

Treatment of anorexia is often overlooked. It is a major feature of many malabsorption states, and patients need to be encouraged to eat as part of their treatment. Moreover, malnutrition should not be attributed solely to malabsorption in conditions where anorexia predominates. For instance, in congestive cardiac failure, minor degrees of malabsorption have been demonstrated, but the wasting in this condition is due to poor appetite and internal metabolic derangement.

TABLE III.—*Treatment*

	Comment
PRIMARY CAUSE	
Elimination Diets	May need ancillary therapy.
e.g.—Gluten	
Milk	
Monosaccharide	Involves extensive carbohydrate restriction.
Curative Therapy	
e.g.—Broad-spectrum Antibiotics	Stagnant loop, Whipple's, tropical sprue, etc.
Anthelmintics	
Excision of blind loop	
Removal of endocrine cause	
Replacement Therapy	
e.g.—Pancreatic extracts	Preparations vary in potency. Effect is unpredictable. Need large frequent doses.
Bile salt preparations	Rarely feasible clinically.
CORRECTION OF MALNUTRITION	Combine with low fat diet.
Calorie—High Carbohydrate	Calorie source.
High Protein	
Medium Chain Triglycerides	Well-absorbed iso-caloric substitute.
Specific Nutrients*	
(a) Potassium	Oral dose variable: 10–50 mEq daily. IV slowly in emergencies.
(b) Calcium	12–16 g. gluconate daily.
(c) Vitamin D	Initial: 100,000 U IM weekly. Maintenance: 100,000 U IM monthly.
(d) Magnesium	Urgent: 3–6 ml. 50% mag. sulph. IV or IM. Can also use oral preparations.
(e) Iron	Various
(f) Folic Acid	5–15 mg. daily.
(g) Vitamin B_{12}	100 µg IM monthly.
(h) Vitamin K	Urgent: 1–5 mg. IM phytomenadione. Daily: 5–20 mg. oral acetomenaphthone.
SYMPTOMATIC	
Low fat diet (30–40 g.	Diminishes steatorrhoea and diarrhoea. Reduces loss of Ca, Mg, etc.
Codeine phosphate	60–240 mg. daily.
Propantheline bromide	45–135 mg. daily.
Kaolin, Tinct. belladonna, etc.	

* Vitamins A, C, and B complex are usually supplied by a normal diet.

Low residue diets for the treatment of diarrhoea are potentially dangerous, since they lack many essential nutrients such as folic acid, and in the presence of malabsorption will aggravate deficiencies.

Medium-chain triglycerides are a recent useful addition to the therapy of fat malabsorption, but their use is limited by expense. These fats are composed of fatty acids which contain only 8 to 12 carbon atoms and are therefore relatively more water-soluble. The intestinal mucosa has a greater capacity for their absorption than for the usual dietary triglycerides. Bile salts and chylomicron formation are unnecessary for absorption, and hydrolysis is very rapid. The resulting fatty acids are transported by the portal vein instead of the lymphatics. They provide a concentrated source of calories that is readily absorbed and therefore diminish the gastrointestinal and metabolic effects of steatorrhoea. They are clearly of benefit in any form of malabsorption, but their use should be restricted to malabsorption states in children with growth retardation, adults for whom there is no specific therapy for the underlying disease, the "short bowel syndrome," and in lymphatic obstruction. They may also be added to a rigid low fat diet to make it more palatable, since they can be used in cooking or salad dressing.

Patients should be seen regularly after diagnosis so that clinical and biochemical improvement can be monitored and any new deficiencies diagnosed and treated.

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